## REMARKS

Claims 1-53 are pending in the application. Applicant acknowledges withdrawal of the rejection claim 54 under §102(b), the rejection of claims 7, 12, 14, 15 and 45 under §103(a) and the rejection of claim 22 under §112, second paragraph. Claims 1, 33 and 40 have been amended. Support for the amendment of claim 1 can be found, for example, at page 6, lines 7-15, page 10, lines 3-7, page 21, lines 1-4 and page 29, lines 3-16, as well as claims 23-27, 29 and 30.

**Withdrawal of Consideration of Claims as Non-elected Species**

The examiner has withdrawn claims 8-13, 15-22, 27, 28, 30, 33-35, 42-44, 47 and 48 from consideration because they do not read on the elected species, *i.e.,* enzyme: carboxylesterase, prodrug: CPT-11, target site: CEA antigen, therapeutic agent: camtothecin. Applicant respectfully traverses the withdrawal of consideration to the extent to claims 30, 33-35 and 44.

More specifically, claim 30 is specifically directed to a method using CPT-11 that is the elected prodrug. Contrary to the examiner's understanding, as explained below, claims 33-35 still involve using a prodrug in step (e). The elected therapeutic agent, camtothecin, is enumerated as one of drugs in the specification. See page 30, lines 7-14. Thus, claim 44 that is directed to a method using a drug as a therapeutic agent reads on the elected species. Accordingly, Applicant respectfully requests the examiner to include claims 30, 33-35 and 44 into the consideration.

**Priority**

The examiner previously accorded claims 1-6, 11, 16-18, 20, 31-34, 36, 39, 42-44, 46 and 49-52 an effective filing date of the grandparent application, April 18, 1988, but now changed her position not to accord any pending claims the earlier filing date. More specifically, the examiner contends that parent application, 08/445,110, which is a continuation of the grandparent application, fails to describe the full scope of compounds encompassed by the phrase "multiple targeting protein" or "targeting protein-enzyme conjugate," which are, for example, "conjugates of single chain antibodies or fusion proteins."

However, the examiner fails to fully understand the disclosure of the parent application in view of the statement that "the parent application confines its description to bispecific antibodies made by covalent conjugation of two antibodies or two antibody subfragments derived from papa in digestion, and to bispecific antibodies made by the polydoma technique."

Contrary to the examiner's understanding, the specification of the (grand)parent application discloses that monoclonal antibodies are also prepared by "more unconventional methods such as interspecies fusions and **genetic engineering manipulations of hypervariable regions**." See page 6, lines 14-16. It is well known at the time of filing of the parent application that monoclonal antibody prepared by the genetic engineering manipulations include single chain antibodies and related constructs. Furthermore, the parent application specifically mentioned that "bispecific antibodies can be made by ...fusions of more than one clone to form polydomas that produce immunoglobulins having more than one specificity, and by genetic engineering." See page 7, lines 28-30. A skilled person in the art would readily understand that this disclosure clearly refers to generically engineered multispecific constructs with single chain antibodies or binding moieties from different immunoglobulins as new fusion constructs.

This conclusion is further supported by the examiner's own statement made for the obviousness rejection that "hybrid or bispecific antibodies that are fusion proteins or conjugates comprising single chain antibodies are known in the art as evidenced by the teachings of King." See page 8, lines 4-1 from the bottom of the Office Action.

In addition, the specification of the (grand)parent application discloses at, *e.g.*, page 8, line 21 through page 9, line 14, methods to covalently link an antibody to an enzyme, which shows that the application filed April 18, 1988, discloses fusion proteins comprising a targeting protein and an enzyme.

In determining whether to satisfy the written description requirement, the examiner has the initial burden of presenting evidence or reasoning to explain why persons skilled in the art would not recognize in the disclosure a description of the claimed invention. The subject matter of claim need not be described literally in order for the disclosure to meet the description requirement. See MPEP 2163. 02 and 2163.04

The examiner, however, fails to meet the initial burden because of misunderstanding of the disclosure of the application filed April 18, 1988. Rather, the close review of the specification leads to the conclusion that the disclosure of the (grand)parent application "reasonably" conveys to the artisan that Applicant was in possession of the claimed invention

as of filing date of the grandparent application, April 18, 1988. Therefore, Applicant respectfully requests that at least claims 1-6, 11, 16-18, 20, 31-34, 36, 39, 42-44, 46 and 49-53 be accorded an effective filing date of April 18, 1988.

**Rejection under 35 U.S.C. § 112, second paragraph**

The examiner has maintained the rejection of claim 23 under 35 U.S.C. § 112, second paragraph, as indefinite. The examiner questions whether claim 1 provides for a second substance. The examiner newly has rejected claim 24 as indefinite alleging that claim 24 is drawn to a method where more than one substance is targeted, while claim 1 recites targeting only one substance. Claims 25-27, 29 and 30 have been rejected because they are drawn to methods where more than one enzyme is administered, whereas claim 1 recites a method where only one enzyme is administered.

While not acquiescing to the examiner's position in these rejections, Applicant obviates these rejections by amending claim 1 specifically recite to "at least one substance" and "at least one enzyme," which clarifies that claim 1 encompasses a method targeting a second substance and/or administering more than one enzyme. The amendment of claim 1 is supported by not only claims 23, 25-27, 29 and 30 but also the disclosure of the specification, for example, at page 6, lines 7-15. Accordingly, Applicants respectfully submits that the amendment of claim 1 renders moot the indefiniteness rejections of claims 23, 25-27, 29 and 30, and thus withdrawal of the rejection is requested.

The examiner has rejected claim 33 as indefinite because the purpose of step (e) is not clear in claim 33 that is drawn to a method where the therapeutic agent is already present by the action of step (c). Applicant respectfully traverse this rejection.

As described in the specification, claim 33 is directed to a method wherein the targeting protein-enzyme conjugate comprises at least one therapeutic agent different from the therapeutic agent of the prodrug used in step (e). The specification clearly states that this method is for addressing the problem of tumor heterogeneity by delivering at least two different therapeutic agents having different tumor-killing properties to the tumor sites. See page 29, lines 3-13. Although the original claim 33 is clear enough to define such a method, in an effort to attend to the examiner's concern, Applicant has amended claim 33 to clarify that the recited therapeutic agent is different from a therapeutic agent of the prodrug used in step (e). Thus, Applicant respectfully requests withdrawal of the rejection of claim 33.

Claims 40 and 41 have been rejected as indefinite for the lack of antecedent basis. Applicant respectfully submits that amendment of claim 40 renders this rejection moot, and therefore withdrawal of the rejection is requested.

**Rejection under 35 U.S.C. § 103(a)**

The examiner has rejected claims 1, 2, 5-7, 14, 45, 46 and 49-52 as obvious over Iwasa in view of Bosslet *et al.* (Bosslet) or Blakey *et al.* (Blakey), and further in view of Potter *et al.* (Potter). Applicant respectfully traverses the rejection.

As a preliminary matter, Applicant submits that none of the cited references is prior art against at least claims 1, 2, 5, 6, 46 and 49-52 because, as previously explained, these claims should be accorded an effective filing date of the grandparent application, April 18, 1988, which antedated the dates of all the cited references. Accordingly, withdrawal of the rejection of these claims is solicited.

With respect to the rejection of claims 7, 14 and 45, Applicant respectfully request withdrawal of the rejection for the reasons that follow.

To establish a *prima facie* case of obviousness, the Examiner must show not only that the art evidences a motivation to have combined the references, as posited, but also that the combination suggests all recited elements. *See* MPEP § 2142. Here, the prior art does not teach or suggest all of the claimed elements. Furthermore, there is no motivation to combine Iwasa with any of the secondary references (*i.e.* Bosslet, Blakey or Potter). Moreover, even if a combination of the prior art could be interpreted to recite each feature of the rejected claims, there is no reasonable expectation of success in arriving at the claimed invention.

For instance, the prior art—either alone or in combination—does not teach:

> at least one multispecific targeting protein comprising at least one first binding site which specifically binds to a substance produced by or associated with the target site and present at the target site and at least one second binding site which specifically binds to an epitope on an enzyme, wherein binding between the targeting protein and the enzyme does not interfere with enzyme activity... [and wherein] the targeting protein binds the enzyme to form a non-covalent targeting protein-enzyme conjugate *in situ*.

The examiner cites Iwasa as a reference teaching a targeting method comprising administering a bispecific antibody that is specific for a target site and specific for an enzyme and administering the enzyme after the bispecific antibody.

Contrary to the examiner's understanding, however, Iwasa does not teach or suggest using a **proagent-activating enzyme** in the context of the present invention. Instead, Iwasa

discloses only bi- or tirspecific antibodies that bind to a target site and directly to a therapeutic agent. In column 3, lines 24-27, Iwasa states:

> ...the present invention provides a hybrid MoAb whose two specificities are respectively against **fibrin** and **thrombolytic substance** and a polydoma which produces this antibody. (emphasis added).

According to Iwasa, the "enzyme" such as urokinase (UK) or streptokinase (SK) is itself a therapeutic agent, *i.e,* thrombolytic agent. See column 4, lines 6-13. Therefore, Iwasa does not teach a multispecific targeting protein such as bispecific antibody according to the present invention that has (1) a specificity for a determinant of a target (2) **a second specificity for an enzyme to convert a proagent to an active agent at the target site**. Therefore, as the examiner also admits, Iwasa is silent to the use a prodrug of a therapeutic agent due to failure to recognize the use of proagent-activating enzyme. That is, Iwasa does not recognize the advantages of the present invention, which provides, in part, for the use of a multispecific targeting protein such as bifunctional antibody to convert a physiologically innocuous proagent into an active therapeutic or diagnostic agent at a target site.

Moreover, a method of Iwasa wherein the enzyme that is a therapeutic agent is administered after the bispecific antibody embodies the problem overcome by the instant invention, namely, delivering an effective amount of therapeutic agent to the target site while minimizing cytotoxicity to non-target cells and tissue. That is, Iwasa provides circulating therapeutic agents in already active form, thereby subjecting patients to potential side effects as a result of non-localized agents.

Accordingly, Iwasa actually teaches away from the present invention, inasmuchas the teachings of Iwasa is directed solely to administration of an active agent without teaching or suggesting of using a proagent-activating enzyme.

The examiner appears to rely on Bosslet, Blakey or Potter as a reference teaching the use of a prodrug, CEA target site and/or CPT-11. However, more importantly, Iwasa disclose neither the use of a prodrug nor the use of an enzyme that converts a prodrug to an active therapeutic agent in the context of the instant invention. Therefore, there is no motivation to combine Iwasa with the secondary references involving the use of a prodrug.

Further, disclosure of Bosslet and Blakey is limited to a conventional covalent linkage between an antibody and an enzyme. Potter merely teaches that a carboxylesterase can activate a CPT-11 prodrug, which, upon activation, is toxic to cells expressing and secreting a carboxylesterase.

Potter, however, does not mention an antibody-enzyme conjugate at all. That is, none of these secondary references teaches or suggests the biding of the enzyme to a targeting protein *in situ*, which is required by the rejected claims. Therefore, the prior art evidences no motivation to combine Iwasa with the teachings of the secondary references.

In this regard, the examiner contends that because Iwasa indicates drawbacks of using antibody-enzyme conjugates where the conjugates are made by covalent linkage between antibody and the enzyme, one of ordinary skill in the art would have been motivated to modify the methods of either Bosslet or Blakey. However, as previously pointed out, the examiner's assertion is derived from the misunderstanding of the methods of Iwasa.

The method disclosed in Iwasa does not use an enzyme converting a prodrug to an active therapeutic agent, but use an enzyme itself as an active agent. Therefore, drawbacks stated in Iwasa is not relevant or sufficient to provide motivation for one of ordinary skilled in the art to modify the methods of either Bosslet or Blakey where an enzyme is used to covert a prodrug to an active therapeutic agent, not used a therapeutic agent itself.

The examiner also has rejected claims 1-7, 14, 45, 46 and 49-52 as obvious over Iwasa in view of either Bosslet or Blakey, and further in view of Potter and further in view of King *et al.* (King). The examiner has rejected claims 1, 2, 5-7, 14, 36-41, 45, 46 and 49-52 as obvious over Iwasa in view of either Bosslet or Blakey, and further in view of Potter, and further in view of Griffiths *et al.* (Griffiths). The examiner further has rejected claims 1, 31 and 32 as obvious over Iwasa in view of either Bosslet or Blakey, and further in view of Potter in view of Sharma *et al.* Claim 53 has been also rejected as obvious over Bosslet or Blakey.

As a preliminary matter, Applicant submits that none of the cited references is prior art against at least claims 1-6, 31, 32, 36, 39, 46 and 49-53 because as previously explained these claims should be accorded an effective filing date of the grandparent application, April 18, 1988, which antedated the dates of all the cited references. Accordingly, withdrawal of the rejection of these claims is solicited.

In traversing the rejection of claims 7, 14, 37, 38, 40, 41 and 45, Applicant submits that the Examiner's reliance on Iwasa as a primary reference is improper for essentially the same reasons described above. Applicant submits that the secondary references do not make up for the deficiencies that exist in Iwasa. The foregoing remarks adequately point out the deficiencies in each of these applied prior art references and Applicant hereby reasserts those deficiencies.

Each of the rejections under 35 U.S.C. § 103 rests upon the determination that one of ordinary skill in the art, as a matter of law, would have been motivated to use the bispecific antibodies of Iwasa in an antibody-enzyme-prodrug application, such as that disclosed by Bosslet or Blakey, further in view of Potter, King or Griffiths, to arrive at the presently claimed invention. However, the prior art fails to evidence any motivation to use bispecific antibodies to form antibody-enzyme conjugates effective for activating a proagent at a target site, as presently claimed.

Applicant respectfully submits that the present invention is based on impermissible hindsight reconstruction, since the only reference that discloses the use of multispecific targeting proteins to specifically bind an enzyme and a target site *in situ*, and to convert a prodrug to an active agent by the enzyme bound to the targeting proteins is the present application. Accordingly, the Examiner has not proven a *prima facie* case of obviousness for any of the claims and a withdrawal of all the obviousness rejections is respectfully requested.

**Obviousness-type double patenting:**

When the other outstanding issues have been resolved, applicant will submit the terminal disclaimer to satisfy the requirements of 37 C.F.R. §§ 1.321 (b) and (c).

**Conclusion**

In view of the foregoing, Applicant submits that all rejections and objections are overcome or are mooted and that the present claims are in condition for allowance. Early notice to that effect is earnestly solicited. Should the Examiner have any questions regarding the present application or believe that further discussion will advance prosecution, the Examiner is invited to contact the undersigned at the telephone number listed below.

Respectfully submitted,

Dec. 31, 2001
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## VERSION WITH MARKINGS TO SHOW CHANGES MADE

Marked up rewritten claims:

1. (Twice Amended) A method for targeting a therapeutic agent to a target site in a patient, comprising the steps of:

(a) administering to the patient an effective amount for targeting of at least one multispecific targeting protein comprising at least one first binding site which specifically binds to [a] at least one epitope of at least one substance produced by or associated with the target site and present at the target site and at least one second binding site which specifically binds to an epitope [on an] of at least one enzyme, wherein binding between the targeting protein and the enzyme does not interfere with enzyme activity;

(b) optionally, administering to the patient an amount effective for clearance of a first clearing composition comprising a clearing agent which clears non-localized targeting protein from circulation;

(c) administering to the patient an effective amount for enzyme activity of the enzyme, such that the targeting protein binds the enzyme to form a non-covalent targeting protein-enzyme conjugate *in situ*;

(d) optionally, administering to the patient an amount effective for clearance of a second clearing composition comprising a clearing agent which clears non-localized targeting protein, non-localized enzyme, or non-localized targeting protein-enzyme conjugate from circulation;

(e) administering to the patient at least one serum-soluble prodrug composition, wherein the enzyme administered in step (c) acts on the prodrug to release a therapeutic agent that is less soluble in serum than the prodrug, and wherein the therapeutic agent partitions out the target site that it accretes at the target site to a greater extent than would the prodrug, thereby providing therapeutic agent at the target site.

33. (Amended) The method of claim 1, wherein the targeting protein, the enzyme, or both, comprises a therapeutic agent such that step (c) results in the *in situ* formation of a targeting protein-enzyme conjugate comprising a therapeutic agent that is different from a therapeutic agent of the prodrug.

40. (Amended) The method of claim 39, wherein at least about 48% of [the] lysine residues of the clearing agent are modified with sugar residues.